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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,787	08/18/2000	Brendan Larder	07691.0005	7344

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	9

DATE MAILED: 02/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,787	LARDER ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3 and 4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group I in Paper No. 6 is acknowledged. The traversal is on the ground(s) that searching all groups would not place a serious burden on the office. This is not found persuasive because the initial isolation procedures to obtain RNA and DNA differ (this is supported by photocopies of the Promega Catalog attached to the instant action), in addition the RNA is extracted from virus isolates while DNA is extracted from different tissue samples therefore the collection techniques would also be different. The inventions group I and group II or group II and group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the claimed nucleotides can also be used as hybridization probes to detect HIV in a sample, which is a materially different process than using the same product in the claimed PCR method.

The requirement is still deemed proper and is therefore made FINAL.

Sequence listing

Applicant needs to provide an updated sequence listing indicating the changes commensurate with the changes in the table.

Information Disclosure Statement

An initialed and dated copy of Applicant's IDS form 1449, Paper No. 3 and 4, is attached to the instant Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The ordinary artisan would not know what is meant by "replaced by one or a pair of replacement primers". The specification does not disclose what is intended by a replacement primer, therefore, the metes and bounds of the instant invention are undefined.

Claims 1, 2, 5, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of the phrase "as represented" is unclear because it is not known if applicant merely intends to use the following sequences as a symbol of what is contemplated as the invention. The dictionary defines represented as: to bring clearly before the mind or to serve as a sign or symbol. Therefore, in regard to the instant claims it is not clear whether the claims intend to be limited the specific sequences recited in SEQ ID NO or if the sequences merely symbolize the potential variety of sequences that may be contemplated for the practice of the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hertogs et al. (Antiviral Agents and Chemotherapy, 1998, IDS paper No. 3) in view of any one of Zazzi et al (Molecular Biotechnology, 1998, paper No. 3), Kozal et al. (U.S.Pat No. 5,856,086), Birk et al. (Aids, 1998), Cabana et al. (Journal of Medical Virology, 1999) or Boden et al. (Journal of the American Medical Association, 1999).

The instant invention is drawn to a method of detecting mutations in the *pol* gene of HIV using a nested PCR reaction, which requires amplification using outer and inner primers, followed by sequencing the amplified region.

Hertog et al. teach a method of detecting the phenotypic resistance with mutation in the HIV *pol* gene starting with an isolated virus. The reference teaches a nested PCR method using the outer primer SEQ ID NO 1 and 2, and a secondary primer. The product of the secondary primer is inserted into a plasmid. For sequencing purposes a 400 base pair fragment of the

protease was amplified and sequenced (see Fig. 6). It is not clear from the reference whether the original nested PCR product, which encode a 2.2 Kb PR-RT coding sequence, is used for the specific PR sequence analysis or if the resulting plasmid was used for the sequencing PR sequencing step. Either way the purpose of the reference is to associate the drug resistance with the nucleotide sequence change. Many drug resistance associated mutations have been located in the reverse transcriptase and protease genes. The reference teaches that it is desirable to determine mutational changes in HIV during treatment in order to adjust treatment protocols. The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Zazzie et al. teaches a nested PCR method using inner and outer primers as well as sequencing primers for the determination of the HIV-1 *pol* genotype (see entire document). The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Kozal et al. teaches a nested PCR method using inner and outer primers as well as sequencing primers for the determination of the HIV-1 *pol* genotype (column 8, lines 26-45). The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Birk et al. teaches a nested PCR method using inner and outer primers as well as sequencing primers for the determination of the HIV-1 *pol* genotype starting from viral RNA samples (see material and methods, and table 1 and 2). The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Cabana et al. teaches a nested PCR method using inner and outer primers as well as sequencing primers for the determination of the HIV-1 *pol* genotype starting from viral RNA samples (see material and methods). The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Boden et al. teaches a nested PCR method using inner and outer primers as well as sequencing primers for the determination of the HIV-1 *pol* genotype starting from viral RNA samples (see material and methods). The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize nested PCR in order to determine mutations in the pol gene of HIV-1 infected individuals. One having ordinary skill in the art would have been motivated to utilize the outer sequences as taught by Hertogs et al. followed by the various inner secondary sequences as taught by Zazzi et al, Kozal et al., Birk et al., Cabana et al. or Boden et al. which amplify different regions of *pol* gene that have been associated with drug resistance. The advantage of the Hertog et al. primer is that it amplifies a large region of the HIV-1 gene providing a larger template to be subjected to the secondary primers allowing for the sequencing of more areas known to contain mutations after drug treatment. The ordinary artisan would be motivated to detect viral mutation early in order to adjust treatment protocols early before allowing the emerging viruses to replicate to great numbers. The association of HIV mutations and inhibitor resistance is well established in the prior art see Zazzi et al, Kozal et al., Birk et al., Cabana et al. and Boden et al. Due to the multiple mutations that are associated with drug resistance, multiple analysis of single *pol* codons is not feasible, thus sequencing the *pol* region which contains the potential drug resistance mutations is the only method allowing proper estimation of *in vivo* drug susceptibility based on the analysis of the viral genotype (Zazie et al., see introduction).

Although the specific sequences of SEQ ID NO: 3-11 have not been disclosed in the prior art for the same purpose, the sequences that are disclosed in the prior art are functional equivalents of the instant sequences. The MPEP 2144.06 provides that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). The specification does not provide the supporting rational for the obviousness rejection. Here the equivalence is related to the end product which is the determination of mutations in the *pol* gene, although the prior art does not teach the specific primers disclosed in SEQ ID Nos: 3-12, one having ordinary skill in the art would have already been directed to the 2.2 kilo base product from the outer primers disclosed by Hertzog et al. Zazzi et al. indicate that sequencing of this region is necessary for the determination of mutation in the *pol* region. In addition, the other cited references provide ample primers that detect smaller regions within the 2.2 kilo base product, all of which would produce the equivalent result of sequencing the regions associated with high mutation rates. If applicant's specific sequences produce an unexpected result, applicant needs to point out what those results are.

Therefore, the instant invention is rejected over Hertogs et al. in view of any one of Zazzi et al., Kozal et al., Birk et al., Cabana et al. or Boden et al.

Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hertogs et al. (Antiviral Agents and Chemotherapy, 1998, IDS paper No. 3) in view of Demeter et al. (Journal of Virological Methods, 1998, IDS #3).

The instant invention is drawn to a method of detecting mutations in the *pol* gene of HIV using single/primary PCR reaction, which requires amplification of the RNA isolated product.

Hertog et al. teach a method of detecting the phenotypic resistance with mutation in the HIV *pol* gene starting with an isolated virus. The reference teaches a nested PCR method using the outer primer SEQ ID NO 1 and 2, and a secondary primer. The product of the secondary primer is inserted into a plasmid. For sequencing purposes a 400 base pair fragment of the protease was amplified and sequenced (see Fig. 6). It is not clear from the reference whether the original nested PCR product, which encode a 2.2 Kb PR-RT coding sequence, is used for the specific PR sequence analysis or if the resulting plasmid was used for the sequencing PR sequencing step. Either way the purpose of the reference is to associate the drug resistance with the sequence change. Many resistance associated mutations have been located in the reverse transcriptase and protease genes. The reference teaches that it is desirable to determine mutational changes in HIV during treatment in order to adjust treatment protocols. The reference does not teach the sequences disclosed in SEQ ID No. 3-12.

Demeter et al. teaches using PCR to determine mutations in the HIV *pol* region and directly sequencing the PCR products (see sequencing methods). The reference teaches numerous primers that may be utilized for the original PCR step and the subsequent sequencing step. The reference does not teach utilizing the primers set out in SEQ ID 1-12.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize PCR in order to determine mutations in the *pol* gene of HIV-1 infected individuals. One having ordinary skill in the art would have been motivated to utilize a single PCR product for sequencing purposes in order to reduce the steps in the laboratory procedures.

The advantage of the Hertog et al. primer is that it amplifies a large region of the HIV-1 gene, covering more areas affected by mutations in response to drug treatment. The choice of sequencing primer will determine which area of the gene is analyzed. Detemer et al. teach numerous primers which can be used to amplify or sequence different regions of *pol* gene associated with drug resistance. Once the gene has been amplified the sequences can be analyzed by using different primers. The ordinary artisan would be motivated to detect viral mutation early in order to adjust treatment protocols before allowing the emerging viruses to replicate to great numbers. Due to the multiple mutations that are associated with drug resistance, multiple analysis of single *pol* codons is not feasible, thus sequencing the *pol* region which contain the potential drug resistance mutations is the only method allowing proper estimation of *in vivo* drug susceptibility based on the analysis of the viral genotype.

Therefore, the instant invention is rejected over Hertogs et al. in view of Demeter et al.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JEFFREY STUCKER
PRIMARY EXAMINER